REMARKS

Applicant appreciates the telephonic interview granted Applicant's representative on January 21, 2004.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Claim 1 is currently amended as discussed with the Examiner, and now specifies at least 75% sequence identity with the specified natural receptor domain sequences.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-11 and 42-62 are now pending in this application.

The claims currently under consideration concern fusion receptors, typically chimeric receptors, in which receptors that include domains of one or more of mGluR, CaR, and $GABA_B$ receptors are fused with a G-protein. The present G-protein fusion receptors can be advantageously configured for use in compound screening to identify compounds that activate the receptor signal through a linked G-protein. Particularly advantageously, such fusion receptors allow signal tranduction switching, where particular receptor sequences are linked with a "non-natural" G-protein, such that a different intracellular signal is produced. For example, most of the mGluR types couple with a G-protein that affects adenylate cyclase. Detection of cellular changes resulting from this linkage is not amenable to high throughput screening. However, if the intracellular domain of a CaR is used, it can be fused to a G-protein that activates phospholipase C, allowing high throughput screening based on intracellular calcium levels.

As indicated above, claim 1 is amended to specify at least 75% sequence identity. Support for this is provided for example at p.3, line 15. Claim 1 is also amended to specify that the domains of the receptor are functionally coupled. Support for this is provided in the specification, for example, at p.6, lines 11-14. Thus, the amendment does not constitute new matter.

Rejections under 35 U.S.C. 112 paragraph 1

In the Advisory Action, the Examiner indicated that claims 1-11 and 42-46 remain rejected, and new claims 47-62 are also rejected, under 35 U.S.C. 112 first paragraph. The Examiner asserts that Applicant has not shown that receptors with the specified levels of sequence identity can be made while retaining activity. Applicant respectfully traverses these rejections.

In accordance with the discussion in the Telephonic Interview on January 21, 2004, Applicant has amended claim 1 to specify that the G-protein receptor domain sequences have at least 75% sequence identity with the respective mGluR, CaR, or GABA B domain sequences. As Applicant pointed out in the prior Amendment, one of ordinary skill in the art will recognize that functional receptors with this level of sequence identity to wild-type domain sequences can readily be designed and constructed.

Thus, as discussed in the 1/21/04 Telephonic interview, in view of the ease with which others can make trivial variations in a receptor sequence of the type presently identified by Applicant, e.g., making conservative amino acid substitutions or inserting sequences from other G-protein linked receptors, allowing variation of amino acid sequences as specified in the present claims is necessary to provide Applicant with meaningful protection for the invention. Narrowly restricting the sequences would merely invite others to make trivial modifications in order to avoid Applicant's claims. Thus, Applicant requests that the Examiner allow the specified range of variation.

Further, as also discussed in the Telephonic Interview, as soon as possible Applicant will submit a Declaration confirming that functional receptors can be constructed that have a short intracellular domain sequence, i.e., at least 10 amino acid residues in length as specified in claim 1. Applicant appreciates the Examiner's indication that he would consider such a Declaration.

In view of the fact that functional receptors with modified domain sequences and with intracellular domain sequences that may be shortened can be constructed, Applicant respectfully submits that the claims are fully enabled, and requests that the Examiner reconsider and withdraw these rejections.

Rejections under 35 U.S.C. § 103

The Examiner maintained the rejections of claims 1-11 and 42-46, and also rejected claims 47-62 under 35 U.S.C. § 103 as allegedly being obvious over Fuller et al. in view of Bertin et al., and further in view of Negalescu et al. The Examiner asserted that one of ordinary skill in the art would have been motivated to produce a G-protein fusion protein comprising a promiscuous G-protein in order to produce the best chance of identifying functional fusion proteins. The Examiner further asserts that the motivation to combine the references is seen when all the references are considered together. Applicant respectfully traverses these rejections.

Applicant respectfully requests that the Examiner again review the discussion concerning the obviousness rejections in the Amendment submitted August 14, 2003. The following discussion primarily addresses the Bertin et al. reference as discussed in the Telephonic Interview, as that reference was indicated to be the key reference.

As was discussed in the 8/14/03 Amendment, it is not proper to consider all the references together to see whether there is motivation to combine those references. The motivation to combine the references in the first place is a necessary prerequisite to considering them together. The proper inquiry is whether the art provides suggestion or motivation to combine the references in a manner leading to the claimed invention.

In this case, the Examiner asserts that the Bertin et al. reference suggests the use of G-protein fusion receptors as presently claimed, stating that "Given the teachings of Bertin et al. that it is desirable to link the G protein to the GPCR, the artisan would have been motivated to perform this procedure for the present invention to optimize the conditions in order to produce the best chance of identifying these functional fusion proteins."

However, as discussed in the Telephonic Interview, no difficulty in identifying functional fusion receptors has been shown, nor is there difficulty in identifying functional chimeric receptors. Indeed, the Examiner's assertion that creating the fusion receptor "in order to produce the best chance of identifying these functional fusion protein" reverses the necessary order. There must be a motivation to produce the claimed G-protein fusion receptors before anything concerning "the best chance" for identifying functional fusion receptors is relevant at all.

In accordance with the Telephonic Interview discussion, the key reference cited in connection with the issue of motivation to create the presently claimed G-protein fusion receptors is Bertin et al. In this regard, the entire disclosure of Bertin et al. must be considered, not just selected portions. Specifically, Bertin et al. describes a β-adrenergic receptor fused with a G-protein used for analyzing natural interactions between members of signaling pathways. In particular, the reference points out (p.8827, first column) that:

> The signal resulting from the activation of a given receptor with an agonist depends on a complex network of interactions between receptors, α and βγ subunits of G proteins, and effectors, which may vary from cell to cell. ... In addition, ligand dependent activation of single receptors may elicit dual signaling. The branching points that lead to the modulation of multiple effectors after activation of a single receptor have not been completely elucidated. ... The functional consequences of the specific interaction between a receptor and a given G protein subtype are difficult to analyze in intact cells, since most G proteins are ubiquitous.

In view of those complications and difficulties, the authors proposed that "Such receptor-Gα fusion proteins may help to elucidate the complex interactions between members of signaling

pathways and may also constitute a useful tool for studying the effects of single effector activation." (Abtract, last sentence)

Thus, Bertin et al. is concerned with analyzing the natural cellular interactions and effects of receptor activation. The authors were attempting to simplify the receptor system by locking the receptor with a single type of G-protein to facilitate that analysis. This reference provides no description or suggestion to create G-protein fusion receptors as presently claimed that are useful for screening for compounds (generally drug screening". Therefore, there is no suggestion or motivation to combine Bertin in any way with Fuller et al. (which describes chimeric receptors that include mGluR and CaR domain sequences), in view of the fact that the Fuller chimeric receptors are generally intended for compound screening.

Therefore, as previously indicated in the 8/14/03 Amendment, Applicant respectfully submits that the Examiner is improperly using hindsight to combine references to lead to the present invention. In order to properly combine references in establishing a *prima facie* case of obviousness, the Federal Circuit has consistently held that there must be a suggestion or motivation from the art to make such a combination. For example, in *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), the court indicated that "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." Further, in *In re Kotzab*, 54 USPQ2d 1308, 1316 (Fed. Cir. 2000) the court stated that in order "to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant."

Further, in considering whether a suggestion to combine particular references exists, the entire disclosures of the references must be considered, i.e., it is improper to pick and choose portions of the disclosures while ignoring portions that would direct one of ordinary skill in the art away from the claimed invention.

With this in mind, as discussed above, Bertin et al. describes fusion of a specific type of receptor, an adrenoreceptor, to G-protein alpha subunit with which the adrenoreceptor normally associates, in order to isolate the G-protein interaction to the single G-protein as a method of analyzing the pathways activated by the receptor through that G-protein. There is no suggestion to construct G-protein fusion receptors particularly use for compound screening (e.g., receptors as specified in present claim 1), nor is there any suggestion of using mGluR, CaR, and/or $GABA_B$ receptor domains (e.g., as in present claims 57-62). Further, nothing in this reference suggests signal transduction switching or any other use of a non-natural G-protein as specified in present claim 1.

Instead, Bertin focuses completely on analyzing normal signaling pathways, utilizing normally interacting receptors and G alpha proteins; that is the entire purpose proposed. This is not only different from the invention specified in present claim 1, but is actually contrary, because utilizing a non-natural G-protein would defeat the entire purpose of the Bertin work. Such fusions to non-natural G-proteins would be useless for elucidate the pathways which the receptor normally activates, the purpose proposed by Bertin et al.

As a result, in view of the fact that Fuller describes chimeric receptors useful for drug screening that include domains of mGluR and/or CaR, there is no suggestion present to combine Fuller et al. with Bertin et al. for any purpose when the entire disclosures of those references are considered.

Also as previously discussed in the 8/14/03 Amendment, Negalescu et al. does not supply the deficiency, nor do the Kaupmann et al. and Rock et al. references. (In order to avoid excessive repetition, these references are not further discussed herein. Once again, Applicant requests that the Examiner review the Amendment submitted 8/14/03.)

In view of the lack of suggestion or motivation to combine the cited references, Applicant respectfully submits that the Examiner has failed to properly make a prima facie case of obviousness. Indeed, when each of the references is considered as a whole for what they teach to

one of ordinary skill in the art, it is apparent that there is no suggestion or motivation to combine these references in any way that might lead to the present invention.

Therefore, Applicant respectfully submits that the Examiner reconsider and withdraw these rejection.

Applicant respectfully submits that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any additional extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 6 February 2004

By _____

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